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Demonstration of Dose-Response Relationship in Seasonal Prophylaxis of Respiratory Infections with Alpha-2b Interferon

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Recombinant alpha-2b interferon was evaluated in two controlled trials, each lasting for 2 months or more, with different dose levels and schedules of administration. The first study was conducted during a period of transmission of type A (H1N1) and type B influenza. At 2.5×10^6 IU per day, no effect on influenza infection could be detected, but there appeared to be an effect on rhinovirus isolation. During the subsequent autumn 1.7×10^6 IU per day was found to have only a minimal effect on rhinovirus infection (efficacy from 22 to 27%). Under similar circumstances the preceding year, but with a daily dose of 3.0×10^6 IU, efficacy had been 76%. Since there was no evidence of change in rhinovirus strains circulating or their interferon susceptibility, this represented a dose-response relationship. It was possible to evaluate side effects in the 1,200 individuals involved. A lower dose was associated with lower frequency of symptoms of blood-tinged mucus. Persons using a placebo spray had a higher frequency of this side effect than an observed control. Using the spray 5 days a week was no less likely to produce symptoms than everyday use. Once-daily use was less likely to produce side effects than twice-daily use. There was no indication of sensitization when interferon was used for two separate periods of 4 weeks.

Intranasal alpha interferon (IFN-α) has been shown reproducibly to have a prophylactic effect against infection with certain respiratory viruses. Most artificial challenge studies have involved rhinoviruses, and initially large amounts of recombinant IFN-α_{2b}, up to 45×10^6 IU per day in divided doses, were employed. Although the prophylactic effect was clear at these levels, side effects involving nasal irritation were encountered, especially when the drug was used for prolonged periods (6, 10, 17). Such prolonged use would be necessary to achieve protection of high-risk individuals throughout seasons of rhinovirus activity (9). Progressively lower doses have been examined in experimental studies to find a prophylactic window, that is, a regimen which would have acceptable efficacy without unacceptable side effects. The challenge studies were carried out for short periods, but the investigators involved felt that the side effects they observed in using the same doses for periods of 26 days without viral infection paralleled in magnitude the prophylactic effect they had documented (15, 16).

Field studies involving natural infection have also indicated that the 10×10^6 IU dose is unacceptable for prolonged use because of side effects (4). At lower doses, there has been less consistency in results, with some studies suggesting that a prophylactic window might exist and others suggesting the opposite. For example, one study at 2.5×10^6 IU daily was terminated after 12 days because of side effects without demonstration of efficacy, whereas another at 2.0×10^6 IU was carried out with definite prophylactic effect demonstrated (2, 7). We recently conducted a field trial with 3.0×10^6 IU of IFN-α_{2b} in divided doses which demonstrated 76% efficacy in prevention of rhinovirus infection as well as a clinical effect against parainfluenza infections. At the same time, a pilot study suggested that a single daily dose might produce fewer side effects (13). We now report further trials of intranasal IFN-α_{2b} with different dosage amounts and schedules of administration.

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MATERIALS AND METHODS

Three studies were conducted at the University of Michigan to evaluate prophylactic and side effects of IFN at various dosage levels and schedules of administration; all involved seasonal use of the drug. The results of the first study conducted in the autumn of 1983 have already been reported (13). This trial lasted 28 days; 200 students were assigned to receive a total of 3×10^6 IU twice daily, 200 students received placebo on the same schedule and 75 students each received 2.5×10^6 IU or placebo once daily. The results of this study will be described here for purposes of comparison. The second study, conducted in the winter of 1983 to 1984, again had a group administering the spray twice daily and the other administering it once daily; the dose in the twice-daily group was 2.5×10^6 IU per day, and that in the once-daily group was 1.9×10^6 IU. The once-daily group stopped using the spray after 28 days. However, the twice-daily group, after a rest period of 14 days, was asked to resume drug or placebo administration on the same schedule for an additional 28 days. In each group, 200 persons were on the drug and 100 were on a placebo, making a total of 600 participants. Finally, in autumn 1984, a study was undertaken with three groups. The first again involved the twice-daily dosage schedule with the first period of spraying lasting 4 weeks (daily dose, 1.7×10^6 IU). After a week without spraying, another period of 3 weeks of use followed. The second group also sprayed twice daily (same daily dose), but only for the 5 week days in a week. This group administered the prophylactic or placebo spray continually during the 8 weeks. With each of these regimens, 150 persons used the drug and 100 used a placebo. An additional 100 persons who did not spray at all were followed over this 8-week period; they were simply observed and specimens were collected by methods identical to those employed with the other groups.

In all three studies, recruitment, instruction, and surveillance of illness in participants and methods of specimen collection and virus isolation were similar to the study previously reported (13); details will not be repeated here.

Blinding was maintained wherever possible, although when varied schedules were involved that difference could be recognized by both investigators and participants. At the pretrial visit, an initial blood specimen was collected and a nasal examination was performed. Participants were instructed on the use of the intranasal spray and tested on its proper use. Each week, participants returned to the clinic on a predesignated day, the symptom card was checked, another card and nasal spray were issued, and the nasal examination was carried out. The returned container of spray was inspected as a measure of assessing compliance. When a period without therapy was part of the design, the same procedures were carried out with the exception of instructions for use of the spray. At the close of a period of observation, a second blood specimen was obtained. When spraying began again, a third specimen was collected after that period of observation. During the third trial, nasal washes were performed at the close of the study for assay of anti-IFN antibody; the method used was that described by Meschievitz et al. (11). Throughout the evaluation, participants were asked to come to the office if they thought they had an acute respiratory illness. A throat and nasal swab for isolation of virus was obtained; a special honorarium payment was given for this visit to assure completeness of specimen collection.

RESULTS

Winter 1983 to 1984: virologic efficacy. This investigation was designed to determine the efficacy of IFN-α_{2b} against natural infection with influenza. During the study period, an outbreak of modest size, mainly of type A (H1N1) influenza, occurred in February and March 1984, followed by a small number of type B infections. Prophylaxis began after influenza virus activity was detected during an initial period of surveillance. The peak of type A transmission occurred in the first cycle of prophylaxis, in which persons were on both once- and twice-daily schedules. Most of the type B activity occurred in the second cycle, when only the latter regimen was in use; at that time, rhinoviruses also began to reappear. The isolation results for influenza viruses and rhinoviruses are shown in Table 1. Because of likely incubation periods, when a virus was isolated during the first 2 days after start of prophylaxis in either cycle 1 or 2, it was excluded from consideration (19). Similarly, isolates from specimens collected for 2 days after prophylaxis ceased would be eligible for inclusion. On the twice-daily schedule, although the differences were in favor of IFN for both type A (H1N1) and type B influenza, the numbers were small and any efficacy, if present, was minimal. In contrast, even with the small numbers, there was a clear suggestion of efficacy for rhinoviruses (no isolation in the IFN group versus 6.0% in the placebo group with both cycles combined). The other viruses isolated were adenovirus and parainfluenza type 1 during the first cycle and parainfluenza type 1 and respiratory syncytial virus during the second cycle. Overall only the difference in total isolation rates in the second cycle was statistically significant ($P < 0.05$), which in large part reflected the effect against rhinoviruses. With the once-daily dose, isolations were slightly less frequent.

Three blood specimens were collected from the group on twice-daily prophylaxis: before cycle 1, between cycles, and 2 weeks after cycle 2. Serum was tested for rises in antibody titers for influenza A (H3N2), A (H1N1), and B and respiratory syncytial virus. No differences in infection rates were found, which is not surprising in view of the known lesser effect of prophylactic agents such as amantadine in protecting against infection rather than symptomatic disease (1, 14). No anti-IFN-α_{2b} antibody could be detected in any post-prophylaxis serum specimens.

Side effects during winter trial. The side effects most often reported in past studies involving seasonal use of intranasal IFN-α_{2b} have been blood-tinged mucus and dry nose (13). Again these symptoms were present in both groups and were more frequently reported among those on prophylaxis than among those receiving placebo. For those on the twice-daily schedule, at some time during cycle 1, 111 or 56% of those receiving IFN reported blood-tinged mucus compared with 22 (22%) of those on placebo ($P < 0.05$). For dry nose the numbers were 67 (34%) and 25 (25%), respectively (differences not statistically significant). Reports of side effects in the two groups dropped sharply in the period off prophylaxis and, in the second cycle, returned to similar levels for blood-tinged mucus but not as high for dry nose. There was no evidence of increased sensitization during the second period of prophylaxis. In addition to the schedule used, the once-daily group also differed in that the total daily dose was somewhat lower. Comparable figures for side effects during the 4 weeks of prophylaxis were 79 (40%) versus 16 (16%) for blood-tinged mucus ($P < 0.05$) and 60 (30%) versus 21 (21%) for dry nose. These cumulative values are lower than those for the first cycle of the twice-daily regimen, but even more dramatic differences can be seen when the prevalence of symptoms on a weekly basis is examined. These values are shown in Fig. 1 for the 6 weeks of observation of the daily dose group and the first 6 weeks of the twice daily dose group; only during the first 4 weeks was drug or placebo administered. Of particular interest is the difference between the two IFN prophylactic schedules indicating, based on the prevalence data, that symptoms among those on the daily dose did not persist as long; this observation can be confirmed if new occurrences of the symptom are examined. However the differences between the two placebo groups

TABLE 1. Isolations of influenza and rhinoviruses during the winter (1983 and 1984) trial of intranasal IFN-α_{2b}

Dose	Cycle	Treatment (*n*)	Isolations [no. (%)]				
			Influenza virus		Rhinoviruses	Other viruses	Total
			Type A (H1N1)	Type B			
Twice daily (2.5×10^6 IU per day)	1	IFN (200)	6 (3.0)	0	0	2 (1.0)	8 (4.0)
	1	Placebo (100)	5 (5.0)	0	1 (1.0)	0	6 (6.0)
	2	IFN (177)	0	2 (1.1)	0	1 (0.6)	3 (1.7)[a]
	2	Placebo (87)	1 (1.1)	2 (2.3)	5 (5.7)	3 (3.4)	11 (12.6)[a]
Once daily (1.9×10^6 IU)	1	IFN (200)	5 (2.5)	0	1 (0.5)	2 (1.0)	8 (4.0)
	1	Placebo (99)	2 (2.0)	0	0	1 (1.0)	3 (3.0)

[a] $P < 0.05$ by the Fisher exact test.

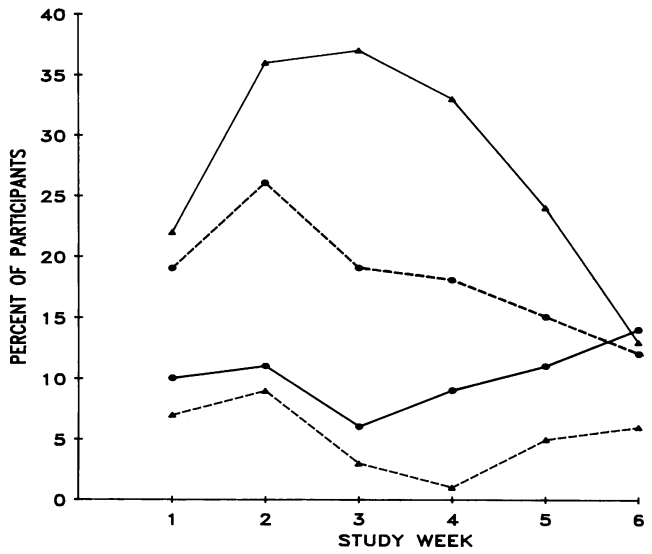

FIG. 1. Weekly prevalence of blood-tinged mucus among persons using intranasal IFN-α_{2b} or placebo. Symbols: ▲———▲, IFN twice daily; ●- - -●, IFN once daily; ●———●, placebo twice daily; ▲- - -▲, placebo once daily.

are also of note, suggesting that nasal spraying even with an inactive compound may be responsible for production or recognition of symptoms.

As in previous studies, abnormalities were occasionally seen on nasal examination, but the numbers were too small for clear determination of patterns. It was not possible to demonstrate symptomatic benefit during this trial.

Autumn trial, 1984 and 1985. The final trial of seasonal prophylaxis was designed to examine effects of different treatment regimens during a period of high rhinovirus prevalence. However, the dose used as determined by bioassay was actually 1.7×10^6 IU daily, instead of the planned amount of 2.5×10^6. Results based on viral isolation are shown in Table 2, limited to rhinoviruses which constituted 92% of all viruses recovered. For comparability, Table 2 is divided according to prophylaxis cycle. However, it should be noted that the "week off" applies only to the group who sprayed twice daily every day; the group who sprayed 5 days a week did so continuously for the entire 7 weeks, and the control did not spray at any point during those weeks. Most of the rhinovirus outbreak occurred during the first 4 weeks (86 of the 108 isolates, or 80%; Table 2). It is during this period that efficacy calculations can best be made to quantify reduction in rhinovirus infection. The protective efficacy was 27% for the once-daily regimen and 22% for the group treated 5 days per week. The highest isolation rates were consistently in the control group. These differences were too small to be statistically significant, and certainly the difference in efficacy between the 5-day and every-day groups cannot be taken to indicate even a trend. However, these efficacy rates are both appreciably lower than the 76% observed the year before when IFN-α_{2b} was administered for 4 weeks on the same every-day schedule.

The higher isolation rates in the controls are an interesting finding. Since members of this group knew they were not receiving any drugs they might have reported illness more frequently, which would have produced such a result. In fact, the overall culture frequency, although highest in the daily IFN group (97 or 66% of participants), was second highest in the control group (59 or 59%). It was lowest in the group receiving placebo daily (42 or 42%).

Ten additional viral isolates were made from the various groups during the 7-week period; of these, seven were parainfluenza viruses. No differences in isolation rates were observed among the various regimens. No anti-IFNα_{2b} activity was demonstrable in the serum or nasal wash specimens collected.

Side effects in autumn of 1984 and 1985. At the dosage level of IFN-α_{2b} used, there was sharply reduced efficacy compared with that seen previously. Side effects were also lower, even with prolonged administration. For those on the twice-daily schedule with no weekend rest period, 32% reported blood-tinged mucus at some time during the first 4 weeks, as compared with 15% in the controls. For the intermittent schedule the results were similar, 35 and 16%, respectively. The differences between the prophylaxis and placebo groups were statistically significant ($P < 0.05$) in both instances. During the same period, the control group reported nasal bleeding in 7% of cases. Over the full 8 weeks, including the week off spraying in the group on continuous prophylaxis, the respective results for blood-tinged mucus were 38 and 19% (continuous IFN and placebo), 43 and 24% (intermittent IFN and placebo), and 7% (observed control). Thus there was no indication that the intermittent schedule was beneficial in terms of side effects. However, overall these frequencies are lower than those seen in the prior trial, probably a result of the lower dose. Also of interest is the much lower frequency of reports of blood-tinged mucus in the observed control group than in the placebo groups. Throughout, the weekly reports of the symptom were similar to these patterns of cumulative prevalence.

DISCUSSION

Two approaches to the control of rhinovirus infection with IFN have been advanced. The first takes advantage of the fact that rhinovirus transmission is most common in a limited period of time during autumn and spring (2, 13). It does not attempt to predict exactly when during these periods the person will be exposed to a rhinovirus infection but envi-

TABLE 2. Recovery of rhinoviruses from IFN and comparison groups, twice-daily dose, autumn 1984

Time period	Recoveries of rhinoviruses [no. (%)] from persons treated as follows:				
	Every day		5 days/wk		Control (100)
	IFN (146)[a]	Placebo (99)	IFN (147)	Placebo (97)	
Cycle 1	15 (10.3)	14 (14.1)	20 (13.6)	17 (17.5)	20 (20.0)
Wk off	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.0)
Cycle 2	4 (2.7)	4 (4.0)	6 (4.1)	1 (1.2)	5 (5.0)
Overall	19 (13.0)	18 (18.2)	26 (17.7)	19 (19.6)	26 (26.0)

[a] Numbers within parentheses in headings indicate *n* for the treatment group.

sions use of the drug regularly during intervals of approximately 6 to 8 weeks. As demonstrated in previous studies, mild side effects often appear, especially after the first weeks of prophylaxis, which largely obscure the demonstration of clinical efficacy of the drug against rhinovirus infection. As a result of these side effects, a second regimen has been tested, use of drug in family members after exposure to a person with a presumed rhinovirus infections (3, 5). In this approach, the drug is employed for only 7 days postexposure, during which period side effects are infrequent, allowing virologic efficacy to be detected clinically. The major limitation of postexposure prophylaxis is its usefulness only against secondary clinical infections acquired in the family. Should an illness be acquired outside the family, or should it follow an inapparent infection within the family, it cannot be prevented. Thus if postexposure prophylaxis is approximately 85% efficacious after a clinical infection but is used after only 30 to 50% of effective exposures, the estimated number of primary infections meeting these conditions (9), its true effectiveness will be 25 to 43%. This estimate is similar to the observed finding in use of postexposure prophylaxis in the natural situation (5). If the purpose of such prophylaxis is to prevent infectious episodes which would trigger acute exacerbations in adults with chronic bronchitis or asthmatic attacks in susceptible children, this level of protection might not be considered acceptable.

It is in just such a susceptible population that IFN-α_{2b} for seasonal prophylaxis would be most attractive for use. There is at present no evidence to suggest that the drug will protect against the acute episode of a chronic respiratory condition, but there is considerable evidence on the role of rhinoviruses in such situations (8, 12, 18). The present report has indicated the daily dose that should be evaluated, 2.5×10^6 IU. No effect against influenza virus should be expected, although some amelioration of symptoms of parainfluenza or coronavirus infection might be anticipated (13, 20). The schedule of administration is still in some question. There is evidence suggesting that a once-a-day dose might be less likely to produce the nasal symptoms than twice-daily doses, but this requires further confirmation because of differences in dosage level. Other methods for reducing side effects might also be evaluated. Side effects in those on placebo were higher than the observed controls, which might be due simply to reporting bias in a nonblinded situation. However, it might equally be related to other factors which could be modified, such as the vehicle or spray device. It should be remembered that the side effects, although present at significant levels, were relatively mild and that no sensitization was found. If it can be shown that IFN-α_{2b} does produce significant reduction in acute exacerbations of chronic respiratory disease or asthmatic attacks, it would be in such situations that the benefits outweigh the side effects.

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